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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 42004

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Application Number: 09/943,334

Filing Date: August 30, 2001

Appellant(s): RITTERSHAUS ET AL.

Leon R. Yankwich

David G. O'Brien

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 24 2004

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the Brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is substantially correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Prior Art of Record

1. Whitlock et a1., J Clin. Invest., 84: 129-37 (1989)
2. Stevens et a1., U.S. Patent 6,143,305
3. Swenson et al., J Biol. Chem., 264(24): 14318-26 (1989)
4. Valmori et a1., J Immunol., 149: 717-21 (1992)
5. Talwar et al., Proc. Natl. Acad. Sci. USA, 91, 8532-8536, (1994)
6. Maillard et al Presse. Med, 29 (31) , 1731-1737, (2000)

The filing date of the US Patent 5,807,552 is August 4, 1995 which is after the filing date of the instant application. Said reference was removed from the rejection under 35 U.S.C. 103(a) over claim 39.

(7) Issues

The appellant's statement of the issues in the brief is correct.

However:

(i) In view of Appellant's persuasive argument relating to enablement rejection under 35 U.S.C. 112, first paragraph with regard to how to make and use an antigenic vaccine peptide, the enablement rejection under 35 U.S.C. 112, first paragraph stands only with regards to a method of preventing atherosclerosis.

(ii) In view of Appellant's persuasive argument relating to the written description rejection with regard to the structure of antigenic peptide, the written description rejection under 35 U.S.C. 112, first paragraph stands only for claims 28 and 29 .

(8) Grouping of Claims

At page 12 of the Brief, Appellant asserts that "with respect to the rejection under 35 U.S.C. 112, first paragraph, relating to enablement , the appealed claims present definitions of varying scope, therefore claims 28, 29, 37 and 38 must be considered separately. Claims 38 and 39 stand or fall together with respect to the issue of enablement".

As has been discussed in Section (7) supra, the enablement rejection under 35 U.S.C. 112, first paragraph now stands only with regard to a method of preventing atherosclerosis. Claims 28, 29 and 37-39 present definitions of the same scope and stand or fall together with respect to issues of enablement.

At page 12 of the Brief, Appellant asserts that "with respect to the rejection under 35 U.S.C. 112, first paragraph, relating to written description, each of the appealed claims defines different embodiments described in different parts of the specification. Therefore, claims 28,29,37,38 and 39 must be considered independently".

As has been discussed in Section (7) supra, the written description rejection under 35 U.S.C. 112, first paragraph now stand only for claims 28 and 29. Claims 28 and 29 defines similar embodiments and stand or fall together with respect to issues of written description.

At page 12 of the Brief, Appellant asserts that " with respect to the rejection under 35 U.S.C. 103(a), claims 28, 29, 37 and 38 stand or fall together. Claim 39 is rejected separately under 35 U.S.C. 103(a) and stands by itself ".

Contrary to Appellant's assertion, claim 39 is a dependent claim of the base claim 28 and defines similar embodiment as the base claim 28. Claims 28, 29 and 37-39 stand or fall together.

(9) Grounds of Rejection

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The following grounds of rejection are applicable to the appealed claims:

Issue 1: Enablement/35 U.S.C. 112, first paragraph

Claims 28-29 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating atherosclerosis, comprising administrating an antigenic vaccine peptide, comprising of the amino acid sequence of SEQ ID NO:2 or a dimer thereof or comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, does not reasonably provide enablement for : (A) method for preventing atherosclerosis comprising administrating antigenic vaccine peptide comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, as recited in

claims 28 or 29; or (B) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (C) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (D) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims

The issue is whether or not the claimed method would function for preventing atherosclerosis. The nature of the invention is such that it would require the administration of vaccine peptide to prevent a mammalian subject from having atherosclerosis. However, according to Maillard et al (Presse. Med, 2000, v. 29 pages 1731-1737, see Abstract in particular) there is a lack in effective methods capable of preventing atherosclerosis-related conditions. (see Abstract in particular). Further, the burden of enabling the prevention of a disease (i.e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to atherosclerosis within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds in preventing atherosclerosis. Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

Issue II : Written Description /35 U.S.C. 112, first paragraph

Claims 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Appellant is in possession of : a method for treating or preventing atherosclerosis, comprising administrating an antigenic vaccine peptide, comprising_the amino acid sequence of SEQ ID NO:2 or a dimer thereof or comprising a universal helper T cell epitope portion linked to B cell of the a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1.

Appellant is not in possession of : a method for preventing atherosclerosis comprising administrating vaccine peptide comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, as recited in claims 28 or 29.

The Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Appellant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the Appellant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the Appellant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention a vaccine peptide comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP and production of native antibodies that recognize the subject's own, endogenous CETP, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed method for preventing atherosclerosis comprising administrating vaccine peptide, wherein vaccine peptide comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP which retain the features essential to the instant invention.

A description of what a material does rather than of what it is, usually does not suffice. The patent does nothing more than describe the desired function of the compound called for and contains no information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention. At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work. Inadequate written description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived" *Fiers v. Revel*, 984 F.2d 1164,1171 9Fed.Cir. 1993).

Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of polypeptide sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes it clear that " Appellant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Appellant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Appellant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Issue III : Rejected under 35 U.S.C. 103(a)

Claims 28-29 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitlock et al. (J Clin. Invest.84:129,1 989) in view of the known fact disclosed in the specification on page 2, lines 10-12, Stevens et al.(U.S. patent 6,143,305), Swenson et al (J. Biol. Chem. 264,14318, 1989) and Valmori et al. (J. Immunology 149: 717, 1992).

The claims are examined as they read upon the elected species and are drawn to a method for treating atherosclerosis, comprising administrating a vaccine peptide, comprising a helper T cell epitope portion and CETP B cell epitope portion, wherein T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid (residues 2-15 of SEQ ID NO:2) and B cell epitope portion comprises B cell epitope of CETP (between 6-26 consecutive amino acids of SEQ ID NO:1 or residues 16-31 of SEQ ID NO:2).

Whitlock et al., teach that in vivo administration of CETP neutralizing antibodies leads to an elevation of circulating HDL, elevation in the ratio of circulating HDL to LDL, VLDL and total cholesterol, a decrease in the level of endogenous CETP activity and increase in the level of circulating HDL. Whitlock et al., further teach that an increased of HDL with a decreased of VLDL would lead to decreased of LDL levels which would be beneficial for a decrease in the development of atherosclerosis legions (see entire document and page 129 in particular).

The specification on page 2, lines 10-12, discloses that it is well known that increased levels of circulating HDL is essential in therapeutically treating of atherosclerosis .

The claimed invention differs from the prior art by the recitation of using a vaccine peptide (i.e. active immunization) comprising a T cell epitope derived from Tetanus toxoid conjugated to a B cell epitope derived from the C-terminus of CETP claimed in claims 28 and 29, or a B cell epitope portion comprising 6 to 26 consecutive amino acids of the carboxyl terminal 26 amino acids of CETP (SEQ ID NO: 1) or comprising the amino acid sequence of SEQ ID NO 2, claimed in claims 37-38 instead of using CETP neutralizing antibodies (i.e. passive immunization) in a method for therapeutically treating atherosclerosis.

Swenson et al. teach that the immunogenic peptide CETP-contains a B cell epitope and that administration of this peptide into animals results in production of anti- CETP antibody (see page 14319 in particular). Swenson et al. further teach the criticality of the carboxyl terminal 26 amino acid sequences derived from CETP, for the elicitation of antibody which decreases the level of endogenous CETP activity (see abstract and entire document). The carboxyl terminal 26 amino acid sequence of CETP is 100 % identical to SEQ ID NO: 1 of the instant application. Thus, Swenson et al. teaches a immunogenic peptide that is the exact the same length and composition as amino acid sequence of SEQ ID NO:I and the same amino acid sequence as amino acid numbers 16-31 of SEQ ID NO:2. Swenson et al. also teach that the treating of atherosclerosis in human can be generally achieved by modulating the activity of endogenous CETP (see page 14318).

US Patent '305 teaches administration of an antigenic vaccine peptide comprising modified polypeptide, i.e. antigen-tetanus toxoid conjugates to induce antibody responses for therapeutic effects. US Patent '305 teaches that said active immunization is advantageous over passive administration of the antibody to the antigen because passive immunization procedures cause anti-antibody responses that cause serious side effect reaction upon repeated injection of the antibody (see column 2 in particular). US Patent '305 teaches that it is well known that the advantage of active immunization over passive, i.e. the concept of attempting to actively immunize a mammal against its own "self-antigen" is well known and successfully applied for various classes of endogenous proteins (see columns 6, 10 and 12 in particular). In addition, US Patent '305 teaches adding a C-terminus cysteine onto the antigen so it can be linked to a tetanus toxoid peptide or other carrier (see column 24 in particular). US Patent '305 teaches the conjugation of peptides to carriers to increase the peptides immunogenicity (see column 10 particular). US Patent '305 teaches that it has been discovered by virtue of this invention that it is possible to treat various diseases which are caused or influenced by various polypeptides by active immunization of a male or female animal by the production and use of antigens formed by administration of modified polypeptides. The modification of the polypeptide forms antigens which are then administered into an animal in which immunization is desired (see column 11 in particular).

Valmori et al. teaches that universally antigenic T cell epitopes (a.a. 830-843 and 947-967) derived from tetanus toxoid (the elected T cell epitope) can be used as carriers (helper T cell epitope) for B cell epitope and that such hybrid peptides can be used to elicit antibody production in human and mice (see Abstract and entire document). Valmori et al. also teaches tetanus toxoid peptide that is the same as amino acids 2-16 of SEQ ID NO:2 of the instant application.

Given the teaching of US Patent '305 and Valmori et al. that active administration of antigen-toxoid conjugates elicit antibody production in human and mice and given the teaching of Whitlock et al. that in vivo administration of CETP neutralizing antibodies leads to an inhibition

of CETP activity and increases in the levels of circulating HDL and teaching of Whitlock et al., Swenson et al. and known fact disclosed in the specification on page 2 that increase in the level of circulating HDL is essential in therapeutically treating of atherosclerosis, one ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to therapeutically treat atherosclerosis by administering a vaccine peptide, comprising a helper T cell epitope portion and CETP B cell epitope portion, wherein the T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid and the B cell epitope portion comprises B cell epitope of CETP.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a vaccine peptide comprising a helper T cell epitope portion derived from tetanus toxoid (as taught by Valmori et al. and US Patent '305.) and a B cell epitope portion, comprising the carboxyl terminal 26 amino acid long CETP (as taught by Swenson et al) and use it in the method for therapeutically treating atherosclerosis because administration of such vaccine peptide would induce the generation of neutralizing antibody which would inhibit CETP activity (as taught by Whitlock et al.,) and inhibition of CETP activity would be essential in treating atherosclerosis (as taught by Whitlock et al., the known fact disclosed in the specification on page 2 and Swenson et al).

One of ordinary skill in the art at the time the invention was made would have been motivated to create a vaccine comprising carboxyl terminal 26 amino acid long CETP –tetanus toxoid conjugate taught by the combined references of Swenson et al., Valmori et al. and Stevens et al. with the expectation that administration of such vaccine would elicit immune responses to the CETP component that would inhibit endogenous CETP activity in vivo. Inhibition of CETP activity would have been expected to be useful in therapeutically treating atherosclerosis as taught by Whitlock et al., the known fact disclosed in specification on page 2 and Swenson et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Whitlock et al. (J Clin. Invest.84:129,1989) in view of the known fact disclosed in specification on page 2, lines 10-12, Stevens et al.(U.S. patent 6,143,305), Swenson et al (J. Biol. Chem. 264,14318, 1989) and Valmori et al. (J. Immunology 149: 717, 1992) as applied to the claims 28,29 37 and 38 above, and further in view of Talwar et al. (Proc. Natl. Acad. Sci, 91: 8532-8536 1994)

The teachings of Whitlock et al. (J Clin. Invest.84:129,1989) , the known fact disclosed in specification on page 2, lines 10-12, Stevens et al.(U.S. Patent 6,143,305), Swenson et al (J. Biol. Chem. 264,14318, 1989) and Valmori et al. (J. Immunology 149: 717, 1992) have been discussed, supra.

The combined prior art teachings differ from the claimed invention only by the recitation that vaccine peptide comprises a dimer of immunogenic peptide of SEQ ID NO:2.

Talwar et al. teaches the use of tetanus toxoid as a carrier to elicit immune responses to autoantigens such as human chorionic gonadotrophin. (see page 8532 and entire document). Talwar et al. also teach that peptide vaccine may also consist of a heterospecies dimer of the alpha-subunit of ovine luteinizing hormone and the beta-subunit of hCG conjugated to either of two immunogenic carrier proteins to elicit production of autoantiboies, that specifically react with the particular endogenous protein. Talwar et al., teaches that vaccines comprising dimers of immunogenic peptide are excellent candidates for providing immune protection for human and animals (see page 8536 in particular).

Given the teaching of Talwar et al., that vaccines comprising dimers of immunogenic peptide are excellent candidates for providing immune protection for human and animals and the teaching of Stevens et al. and Valmori et al that active administration of antigen- toxoid conjugates elicit antibody production in human and mice plus the teaching of Whitlock et al. that in vivo administration of CETP neutralizing antibodies leads to an inhibition of CETP

activity and increased in the levels of circulating HDL and the teaching of Whitlock et al., Swenson et al., and the known fact disclosed in the specification on page 2 that increases in the level of circulating HDL is essential in therapeutically treating of atherosclerosis, one ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to use a vaccine peptide, comprising a helper T cell epitope portion and CETP B cell epitope portion, wherein the T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid and the B cell epitope portion comprises B cell epitope of CETP in the method of therapeutically treating atherosclerosis

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct a vaccine comprising a dimer of an immunogenic peptide which will provide immune protection for human and animals (as taught by Talwar et al. and Stanton et al.) wherein said immunogenic peptide comprising a helper T cell epitope portion derived from tetanus toxoid (as taught by Valmori et al.) and a B cell epitope portion, comprising the carboxyl terminal 26 amino acid long CETP (as taught by Swenson et al) with the expectation that administration of such vaccine would induce the generation of neutralizing antibody which would inhibit CETP activity (as taught by Whitlock et al.,) and that inhibition of CETP activity would be essential in treating atherosclerosis (as taught by. Whitlock et al., the known fact disclosed in the specification on page 2 and Swenson et al).

One of ordinary skill in the art at the time the invention was made would have been motivated to create a vaccine which will provide immune protection for human and animals comprising a dimer of an immunogenic peptide (as taught by Talwar et al. and Stanton et al.) wherein said immunogenic peptide comprises carboxyl terminal 26 amino acid long CETP –tetanus toxoid conjugate taught by the combined references of Swenson et al., and Valmori et al. with the expectation that administration of such a vaccine would elicit immune responses to the CETP component that would inhibit endogenous CETP activity in vivo. Inhibition of CETP activity would be expected to be useful in therapeutically treating atherosclerosis as taught by Whitlock et al., the known fact disclosed in specification on page 2, and Swenson et al.

(10) Response to Argument

Issue I: Demonstration and Enablement of Prevention of Atherosclerosis

Claims 28-29 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating atherosclerosis, comprising administrating an antigenic vaccine peptide, comprising_the amino acid sequence of SEQ ID NO:2 or a dimer thereof or comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, does not reasonably provide enablement for : (A) method for preventing atherosclerosis comprising administrating an antigenic vaccine peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion of CETP, as recited in claims 28 or 29; or (B) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising a universal helper T cell epitope portion linked to a B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (C) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (D) method for preventing atherosclerosis comprising administrating vaccine peptide, comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

At page 15 of the Brief, Appellant argues that the subject matter of the appealed claims, i.e. a method of treating or preventing atherosclerosis was resolved in appellant's favor in parent applications: 08/945,289, now US Patent 6,555,113 and 08/432,483, now US Patent 6,410,022. At page 17 of the Brief, Appellant submits that the issues presented in this appeal are not issues that are raised *de novo* in connection with the subject

matter disclosed in the present application but rather are issues already raised in earlier applications.

At page 17 of the Brief, Appellant argues that working examples of the current specification demonstrate the prevention of atherosclerosis.
However, at page 18 of the Brief, Appellant disclosed that the rabbits fed a diet high in cholesterol and that received a CETP vaccine peptide, has a significantly less aortic plaque formation than rabbits that were fed the same atherogenic diet but did not receive the vaccine. Appellant further disclosed that the results shown on Fig. 13, exhibited a statistically significant reduction in the overall occurrence and size of lesions in rabbits that received a CETP vaccine peptide as compare to the extent and size of atherosclerotic lesions in untreated animals. The results demonstrated that administration of a CETP vaccine peptide was capable of retarding the formation of atherosclerotic lesions in animals.

Contrary to Appellant's assertion it is noted that the functional limitations of the present amended claims are different from functional limitations of US Patent '022 claims. For example, claim 18 of US Patent '022 recited only a method of treating atherosclerosis, while the instant claim 28 recites a method of treating or preventing atherosclerosis. In addition, claim 18 of US Patent '022 recited an antigenic vaccine wherein B cell epitope portion comprises six to 26 consecutive amino acids of the carboxyl terminal 26 amino acid of human CETP (SEQ ID NO:1), while the instant claim 28 recited *any* B cell epitope of CETP. The newly cited references raise the new issue that was never addressed in earlier application. US Patent '305 clearly teaches that at the time the invention was made it was well known the advantage of active immunization over passive, i.e. the concept of attempting to actively immunize a mammal against its own , "self-antigen" was well known in the art and successfully applied for various classes of endogenous proteins. This reference was missing in all previous art rejections of record in earlier applications.

The Appellant's statement that " the results demonstrated that administration of a CETP vaccine peptide was capable of retarding the formation of atherosclerotic lesions in animals" supports the Examiner's position that the instant claims are only enabling for a method of treating atherosclerosis because Appellant himself acknowledge that administration of a CETP vaccine peptide was capable of reduction, not completely prevention of atherosclerotic lesions in animals.

In addition, the Specification clearly disclosed that only 5 out of 12 vaccinated rabbits were capable of producing anti-CETP antibody (see example 7 of the Specification as filed in particular). Moreover, the Specification further disclosed that non-vaccinated animals had a lesion that covered an average of 45 % of the total area of the aorta, whereas vaccinated animal had lesions that covered an average 19 % of the total area of the aorta (see page 38 of the specification as filed in particular). One of skill in the art at the time the invention was made would clearly have interpreted these data as *reduction, not completely prevention* of atherosclerotic lesions in animals. Moreover, the current state of the art is that there is a lack in effective methods capable of preventing atherosclerosis-related conditions, as taught by Maillard et al.

At page 20 of the Brief, Appellant argues that the appealed claims do not recite the use of *any* B cell epitope of CETP, rather the claims recite the use of a vaccine peptide, comprised at least two structural components (universal helper T cell epitope and B cell epitope portion) which vaccine peptide is antigenic. As to the selection of the B cell epitope portion, the complete sequence of the human CETP protein is disclosed in the present specification (SEQ ID NO:4), and an entire section of the specification (pp. 12-16) is devoted to describing suitable B cell epitopes of CETP for use in a vaccine peptide according to the invention. All of the information necessary to select B cell epitope candidates, to link them to universal helper T cell epitope portions to form vaccine peptides, and to administer them to human or animals and detect whether they elicit an autoimmune anti-CETP antibody response is provided by Appellants' specification.

This argument is persuasive and obviates the previous rejection of claim 28 and 29 under 35 U.S.C. 112 first paragraph regarding enablement to make and use antigenic vaccine peptide comprising universal helper T cell epitope portion linked to B cell epitope of CETP, the since the specification describes an actual process for selecting and for testing CETP vaccine peptide to determine whether they elicit an immune response against endogenous CETP.

Issue II. Demonstration of the full possession of the Invention at the time of filling.

Claims 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Appellant is in possession of : a method for treating or preventing atherosclerosis, comprising administrating an antigenic vaccine peptide, comprising of the amino acid sequence of SEQ ID NO:2 or a dimer thereof or comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1.

Appellant is not in possession of : a method for treating or preventing atherosclerosis comprising administrating vaccine peptide comprising a universal helper T cell epitope portion linked to any B cell epitope portion of CETP, as recited in claims 28 or 29.

At page 25 of the Brief , Appellant assets that there is an actual reduction to practice of treatment and prevention of atherosclerosis using a vaccine peptide according to the description. The use of the vaccine peptide of SEQ ID NO:2 to inhibit formation of atherosclerotic plaque in the aortas of mammalian subjects is described in detail in Examples 6-10 of the specification (pages 32-38). At page 27 of the Brief Appellant assets that contrary to the Examiner's assertion, Appellants have provided "a recitation of structural features common to the genus" i.e., B cell epitopes and have taught "which features constitute a substantial portion of the genus", i.e., they all must elicit the production of autoantibodies to endogenous CETP when linked with the T cell epitope portion according to the claims.

Contrary to Appellant's assertion in the instant case, there is no described or art-recognized correlation or relationship between the structure of the invention vaccine peptide comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP and its production of native antibodies that recognize the subject's own, endogenous CETP the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed method for treating or preventing atherosclerosis comprising administrating vaccine peptide, wherein vaccine peptide comprising a universal helper T cell epitope portion linked to any B cell epitope portion of CETP which retain the features essential to the instant invention.

A description of what a material does rather than what it is, usually does not suffice. The patent merely describes the desired function of the compound called for but contains no information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention. At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work. Inadequate written description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived" *Fiers v. Revel*, 984 F.2d 1164,1171 9Fed.Cir. 1993).

The claimed composition of matter defined only by its biological activity or function, i.e. elicit production of autoantibodies to endogenous CETP is insufficient to satisfy 35 U.S.C. 112, first

paragraph. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

Issue III. Whether the methods recited in appealed claims would have been obvious to a person of ordinary skill in the art at the time of Appellant's invention.

Claims 28-29 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitlock et al. (J Clin. Invest.84:129,1 989) in view of the known fact disclosed in the specification on page 2, lines 10-12, Stevens et al.(U.S. patent 6,143,305), Swenson et al (J. Biol. Chem. 264,14318, 1989) and Valmori et al. (J. Immunology 149: 717, 1992).

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Whitlock et al. (J Clin. Invest.84:129,1989) in view of the known fact disclosed in specification on page 2, lines 10-12, Stevens et al.(U.S. patent 6,143,305), Swenson et al (J. Biol. Chem. 264,14318, 1989) and Valmori et al. (J. Immunology 149: 717, 1992) as applied to claims 28-29 and 37-38 above, and further in view of Talwar et al. (Proc. Natl. Acad. Sci, 91: 8532-8536 1994)

A. The references relied on by the examiner are improperly combined.

At page 16 of the Brief, Appellant disclosed that during prosecution of grandparent application 08/432,483 the same Whitlock et al., Swenson et al., and Valmori et al., references were also combined in that case to reject the claims as obvious and was reversed by the Board. On overlapping pages 29 –30 of the Brief, Appellant asserts that the concept of attempting to actively immunize a mammal against its own, endogenous CETP is nowhere found in the prior art. That concept is found only in Appellants' specification. Nowhere in this record has the Examiner ever presented the required evidence FROM THE PRIOR ART of a motivation to control CETP activity by active immunization. The only references discussing immunization against a "self ' protein, i.e., Stevens (US Patent '305) and Talwar, do not relate at all to cardiovascular disease and do not mention CETP or atherosclerosis. Neither do they advocate extension of their teachings (relating to human chorionic gonadotropin and maintenance of pregnancy) to any other protein or physical condition. Appellant further points out that the Whitlock reference reports the results of administering a murine anti-human CETP monoclonal antibody (TP1) to rabbits. No rabbit anti-CETP antibodies are generated within the rabbit, by vaccination with a hybrid peptide or any other agent. The reference does not relate to the subject of the present invention, namely, generation of an antibody response to a subject's own CETP by administration of a hybrid peptide according to the claims as a therapeutic agent for the treatment or prevention of atherosclerosis. While Swenson may show the use of xenogeneic human CETP or CETP fragments to immunize mice and raise murine anti-human CETP antibodies for in vitro use (e.g., immunoblots, assays, purification protocols), there is no teaching of raising anti-mouse CETP antibodies in mice or anti-rabbit CETP antibodies in rabbits. Immunization against a foreign CETP has been shown in the references; active immunization against a self CETP has not. On page 31 of the Brief, Appellant further asserts that from no combination of the references is the desirability of CETP as an autoimmune target suggested, and even the presence of a reference

(Stevens) that involves attempts to raise an antigen response to a self antigen does not contain anything to encourage the person of ordinary skill in the art to apply the Stevens disclosure respecting hormones to a completely different class of protein, i.e., a large, constitutively produced, circulating serum protein that plays a role in a complex metabolic cascade, that is, CETP. On page 33 of the Brief, Appellant asserts that the Examiner has fallen into trap of hindsight reconstruction by mentally presuming the existence of a motivation or suggestion to combine all references.

Contrary to Appellant's s assertion, the art rejections in the current prosecution are based on the combination of some of the references of record, i.e. Whitlock et al., Swenson et al., Valmori et al., and newly cited reference i.e. US Patent 6,143,305.

In response to Appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Appellant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971).

Appellant has traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Appellant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

The examiner disagrees with the Appellant's statement that concept of attempting to actively immunize a mammal against its own, endogenous protein is nowhere found in the prior art.

US Patent '305 teaches administration of antigenic vaccine peptide comprising a modified polypeptide, i.e. antigen-tetanus toxoid conjugates to induce antibody responses for therapeutic effects. US Patent '305 clearly teaches that active immunization is advantageous over passive administration of the antibody to the antigen because passive immunization procedures cause anti-antibody responses that cause serious side effect reaction upon repeated injection of the antibody (see column 2 in particular). US Patent '305 teaches that it is well known that the advantage of active immunization over passive, i.e. the concept of attempting to actively immunize a mammal against its own , "self-antigen" is well known and successfully applied for various classes of endogenous proteins (see columns 6, 10 and 12 in particular).

Moreover, contrary to Appellant's assertion, US Patent '305 does not limit the disclosure to immunization against only hormones or does not advocate extension of the teachings (relating to human chorionic gonadotropin and maintenance of pregnancy) to any other protein or physical condition. US Patent '305 explicitly teaches that it has been discovered by virtue of this invention that it is possible to treat various diseases which are caused or influenced by various polypeptides by active immunization of a male or female animal by the production and use of antigens formed by administration of modified polypeptides. The modification of the polypeptides to form antigens which are then administered to an animal in which immunization is desired (see column 11 in particular). US Patent '305 further teaches that the present invention is not limited to modification of protein reproductive hormones and numerous further examples of modification of the non-hormonal endogenous proteins that are large, constitutively produced, circulating serum protein that plays a role in a complex metabolic cascade (see column 10, lines 45-55, column 12, lines 18-65 and overlapping columns 21-22 in particular). Clearly the teaching of US Patent '305 would be " spark of motivation" to one skilled in the art to consider endogenous CETP as a target for endogenous immune regulation. In addition, it is noted that in both passive immunization taught by Whitlock et al., and active immunization taught by current application the motivation was the same – to target the endogenous CETP that would be beneficial in treating atherosclerosis. The means to target endogenous CETP was different. However, one skilled in the art at the time the invention

was made was well aware of the advantage of active immunization over passive, and the ways to overcome immune tolerance of various endogenous, self -proteins as evidenced by the teaching of US Patent '305. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

B. No combination of any of the Examiner's citation shows or suggests successful treatment or prevention of Atherosclerosis.

At page 34 of the Brief, Appellant asserts that : (i) Swenson demonstrates the immunogenicity of human CETP in mice but, the reference falls far short of demonstrating any effect of altered CETP activity on atherosclerosis. (ii) The Whitlock reference describes a short term passive immunization study of CETP activity. The inhibition of CETP activity by passive immuniztion would fall off within a few days, after which CETP activity and cholesterol metabolism in the subject would be the same as before the passive immunization. At page 34 of the Brief, Appellant asserts that nothing from the cited prior art illustrates a method by which the development of atherosclerosis can be checked.

It is noted that the appealed claims are rejected under 35 U.S.C. 103(a) as they read on the method for treating atherosclerosis. As has been addressed supra, in Section 9, issue I, the current state of the art is that there is a lack in effective methods capable of preventing atherosclerosis.

The Examiner disagrees with the Appellant's interpretation of the Swenson references. Swenson explicitly teaches that modulating the activity of endogenous CETP could have an important influence on atherosclerosis (see page 14318, bottom of the right column). With

respect to the Appellant's arguments of short duration of inhibiting CETP activity by Swenson, this argument is not persuasive, since it is well known in the art that when antibodies from one species (i.e. murine monoclonal antibodies) are administered to another species (i.e. rabbit) as was done in Whitlock, the antibodies have a relatively short half-life as compared to antibodies elicited by administration of a vaccine. Foreign proteins such as mouse antibody in a rabbit are eliminated as foreign. However, one skilled in the art at the time the invention was made was well aware of the advantage of active immunization over passive, and the ways to overcome immune tolerance of various endogenous, self -proteins as evidenced by the teaching of US Patent '305. Therefore the increase in duration of modulation of CETP activity using active immunization with antigenic peptide would have been an obvious variation of Whitlock et al., because in both passive immunization as taught by Whitlock et al., and active immunization taught the by current application , the motivation was the same – to target the endogenous CETP that would be beneficial in treating atherosclerosis.

With regard to the issue that nothing from the cited prior art illustrates a method by which the development of atherosclerosis can be checked, it is noted that the Appellant's claims are not drawn to a method by which the development of atherosclerosis can be checked.

C. The evidence of record shows the lack of a reasonable expectation of success in active immunization against self proteins.

At page 36 of the Brief, Appellant asserts that Stevens (US Patent '305) describes vaccine compositions for producing autoantibodies in an individual to inhibit the effect of an intermittently produced hormone. However, no protein mentioned in Stevens has a role in cholesterol metabolism or cardiovascular health. Thus, Appellants submit that a person of ordinary skill in the art would receive no guidance from Stevens that would be considered relevant or applicable to inhibiting CETP activity or treatment of atherosclerosis. Appellant further asserts that no immunologist, least of all the legal standard person of ordinary skill in the art, would equate passive immunization with active immunization; and no immunologist would confuse the immunogenicity of a

foreign antigen with overcoming immune tolerance of endogenous, self proteins. The Examiner evidently asserts that combining Whitlock's study using passive immunization with references such as Stevens makes Appellants' methods that employ active immunization against CETP predictable and, moreover, likely to succeed. However, the fact is that a person of ordinary skill in the art is well aware that passive immunization is NOT a reasonable predictor of active immunization , and vice versa. This lack of predictability between passive immunization and active immunity in an individual is vividly illustrated in Michel et al., (already of record, submitted in Appellant's IDS, in parent application 08/945,289, now Patent 6,555,113). Michel is a published review of over 30 years of immunologic-based biochemical studies of the renin- angiotensin system (RAS). At page 39 of the Brief, Appellant asserts that Michel illustrates how variable results have been in attempts to effectively overcome the tolerance of an individual for a particular self protein in order to elicit production of autoantibodies that effectively bind or inhibit the particular endogenously produced protein target. Accordingly, the passive immunity of the study of the Whitlock reference does not provide a reasonable expectation of success for Appellants' claimed methods that rely on active immunization.

At page 39 of the Brief, Appellant asserts that there is more evidence from the prior art on this record to conclude that active immunization will fail than there is evidence that it will succeed.

US Patent '305 teaches that it is well known the advantage of active immunization over passive, i.e. the concept of attempting to actively immunize a mammal against its own , "self-antigen" is well known and successfully applied for various classes of endogenous proteins (see columns 6, 10 and 12 in particular). However, contrary to Appellant's assertions , as has been discussed supra in Section 4 A, US Patent '305 does not limit the disclosure to immunization against hormones, or does not advocate extension of the teachings to any other protein or physical condition. US Patent '305 explicitly teaches that it has been discovered by virtue of this invention that it is possible to treat various diseases which are caused or influenced by various polypeptides by active immunization of a male or female animal by

the production and use of antigens formed by administration of modified polypeptides. The modification of the polypeptides forms antigens which are then administered into an animal in which immunization is desired (see column 11 in particular). US Patent '305 further teachs that the present invention is not limited to modification of protein reproductive hormones and numerous further examples of modification of the non-hormonal endogenous proteins that are large, constitutively produced, circulating serum protein that plays a role in a complex metabolic cascade (see column 10, lines 45-55, column 12, lines 18-65 and overlapping columns 21-22 in particular).

With respect to Appellant's arguments that Michel teaches that successful use of passive immunization is not predictive of active immunization.

This argument is not persuasive in view of the prior art success in eliciting antibodies to CETP by conjugating CETP B cell epitope to carrier proteins. Appellant on page 30 of the Brief acknowledge that Swenson teaches the use of immunogenic peptide CETP or CETP fragments to immunize a mice. In other words, the prior art teaches the successful use of active immunization with human CETP antigen to produce anti-CETP antibody. Swenson further teaches the criticality of the carboxyl terminal 26 amino acid sequences derived from CETP, for the elicitation of antibody which decrease the level of endogenous CETP activity . The carboxyl terminal 26 amino acid sequence of CETP is 100 % identical to SEQ ID NO: 1 of the instant application. Thus, Swenson teaches a immunogenic peptide that is the exact the same length and composition as amino acid sequence of SEQ ID NO:I and the same amino acid sequence as amino acid numbers 16-31 of SEQ ID NO:2 that was successfully used to generate production of antibody to recognize endogenous CETP. Moreover, Appellant 's argument that Michel et al. teaches that only 1/50 rats were antibodies elicited when immunized with pure rabbit converting enzyme is not on point, since the instantly claimed methods are not drawn to immunizing with intact CETP, but rather to conjugates of CETP B cell epitopes to carrier proteins which are known in the art to increase the efficiency of eliciting antibodies to the epitopes conjugated to the carrier protein.

D. With respect to treatment and prevention of atherosclerosis by active immunization, appellant's results are unexpected and therefore indicative of non-obviousness.

At page 42 of the Brief, Appellant asserts that combined citations would still only lead to the expectation of a transient reduction of CETP activity (e.g., a reduction of only a matter of hours as in Whitlock), which transient reduction would be overcome by clearance of the antibodies or possibly neutralized by upregulation of CETP production in vivo and there is no way for a person of ordinary skill in the art to form an expectation as to the results of vaccination on the extent of development of atherosclerotic lesions, because none of the references includes any teachings that link reduction of CETP activity in plasma with actual reduction in arterial plaque. Thus, Appellants' Example 10 and Fig. 13, which show the effect of their observed degree of modulation of endogenous CETP activity on the treatment and prevention of atherosclerotic lesions, present results that are clearly unexpected and unpredictable on the basis of the prior art. Appellant further argues that actual performance of this work produced an antibody response that was specific and which produced lasting effects on cholesterol and HDL levels that was unexpected and IE a thousand fold duration of CETP modulation as compared to method of Whitlock et al.

This argument is not persuasive, since it is well known in the art that when antibodies from one species (i.e. murine monoclonal antibodies) are administered to another species (i.e. rabbit) as was done in Whitlock et al., the antibodies have a relatively short half-life as compared to antibodies elicited by administration of a vaccine. Foreign proteins such as mouse antibody in a rabbit are eliminated as foreign. Therefore the increase in duration of modulation of CETP activity using the instantly claimed methods versus the method of Whitlock et al. is not an unexpected result. However, one skilled in the art at the time the invention was made was well aware of the advantage of active immunization over passive, and the ways to overcome immune tolerance of various endogenous, self -proteins as evidenced by the teaching of US Patent '305. Clearly the teaching of US Patent '305 would be the " spark of motivation" to

one skilled in the art to consider endogenous CETP as a target for endogenous immune regulation.

Therefore the increase in duration of modulation of CETP activity using active immunization with antigenic peptide would have been an obvious variation of Whitlock because in both passive immunization taught by Whitlock et al., and active immunization taught by current application the motivation was the same – to target the endogenous CETP that would be beneficial in treating atherosclerosis.

Moreover, as acknowledge by the Appellant on page 4 of the Brief, it is well known in the art that decreased susceptibility to cardiovascular diseases, such as atherosclerosis , is generally inversely correlated with increased absolute levels of circulating HDL and also increases levels of HDL relative to circulating levels of VLDL and LDL. Appellant also acknowledges on page 4 of the Brief that high CETP activity are correlated with increased risk of cardiovascular disease. In addition, Swenson also teaches that treating atherosclerosis in human can be generally achieved by modulating the activity of endogenous CETP (see page 14318 in particular).

Therefore, one of ordinary skill in the art at the time the invention was made would have had the expectation that immunizing with a vaccine that elicits an immune response that neutralize CETP activity would treat atherosclerosis.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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